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Characteristics Associated With Delirium in Older Patients in a Medical Intensive Care Unit

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Background: Delirium is a highly prevalent disorder among older patients in the intensive care unit.

Methods: We performed a prospective cohort study of 304 patients 60 years or older admitted from September 5, 2002, through September 30, 2004, to a 14-bed ICU in an urban university teaching hospital. The main outcome measure was ICU delirium that developed within 48 hours of ICU admission. Patients were assessed for delirium with the Confusion Assessment Method for the ICU and medical record review. Risk factors for delirium were assessed on ICU admission by interview with proxies and medical record review. A model was developed using multivariate logistic regression and internally validated with bootstrapping methods.

Results: Delirium occurred in 214 study participants (70.4%) within the first 48 hours of ICU admission. In

a multivariate regression model, 4 admission risk factors for delirium were identified. These risk factors included dementia (odds ratio [OR], 6.3; 95% confidence interval [CI], 2.9-13.8), receipt of benzodiazepines before ICU admission (OR, 3.4; 95% CI, 1.6-7.0), elevated creatinine level (OR, 2.1; 95% CI, 1.1-4.0), and low arterial pH (OR, 2.1; 95% CI, 1.1-3.9). The C statistic was 0.78.

Conclusions: Delirium is frequent among older ICU patients. Admission characteristics can be important markers for delirium in these patients. Knowledge of these admission risk factors can prompt early correction of metabolic abnormalities and may subsequently reduce delirium duration.

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DELIRIUM IS AN ACUTE DISORDER of attention and cognition with a reported prevalence of 78% to 87% among intensive care unit (ICU) patients.¹⁻³ Delirium causes increased morbidity, mortality, nursing home placement, longer ICU and hospital stays, and costlier hospitalizations.^{4,5} In patients who receive mechanical ventilatory assistance, delirium is a predictor of 6-month mortality.⁶ Patients with 1 episode of delirium had a 40% increase in ICU and total hospital costs, after controlling for confounding variables, compared with patients with no delirium.⁷ Moreover, delirium is listed as 1 of the 6 leading causes of preventable injury in those older than 65 years.⁸

Identification of admission risk factors is of crucial importance in identifying patients at high risk for delirium on ICU admission—to target intervention strategies and determine the interaction of baseline vulnerability with precipitating factors. This approach has been applied previously in examining admission and precipitating risk

factors for delirium in non-ICU populations.^{9,10} To date, only a handful of studies have prospectively examined risk factors for delirium in the ICU.¹¹⁻¹³ These studies have shown that age, severity of illness, hypertension, alcoholism, and sedative and analgesic use were associated with delirium, although the studies did not always ensure that the risk factor preceded delirium development.

The aims of our study were to extend the previous work to identify risk factors associated with delirium in older ICU patients based on admission characteristics and to assess the risk of delirium in the presence of multiple factors. Our goal was to provide a means to identify which characteristics are most strongly associated with the occurrence of delirium within the first 48 hours of ICU admission.

METHODS

Study participants were 304 consecutive patients 60 years or older who were admitted to the medical ICU at Yale-New Haven Hospital, New Haven, Connecticut, from September 5, 2002, through September 30, 2004. Yale-New

Haven Hospital is a 900-bed teaching hospital with a 14-bed ICU. Patients were excluded if no identifiable proxy was available to provide information, they died before the proxy interview was obtained, they transferred from another ICU (because of missing admission data), their admission lasted less than 24 hours, or they were non-English speaking. Of the 725 patients screened, 318 were eligible. Reasons for noneligibility included admission for less than 24 hours ($n=193$), transfer from another ICU ($n=83$), inability to communicate before admission (eg, because of aphasia or total deafness) ($n=52$), no identifiable proxy ($n=56$), and being non-English speaking ($n=23$). Of the 318 eligible patients, 309 (97.2%) were enrolled. Of the 9 eligible but not enrolled, 8 exclusions were because of proxy refusal and 1 was because of patient refusal. Five patients had persistent coma during their ICU stay and were excluded from further analysis, reducing our final sample to 304. Informed consent was obtained from the proxy and patient according to procedures approved by the institutional review board of Yale University School of Medicine.

ASSESSMENT OF ADMISSION RISK FACTORS

Because the patients in this study were critically ill, proxy respondents were used as the primary source of information.^{14,15} The research nurse identified a proxy who spent a minimum of 4 h/wk with the patient and who had known the patient for at least 5 years. The proxy was asked whether he or she could assess the patient's functional and mental abilities. A hierarchy of proxies was used that assessed the spouse or live-in partner first, then the live-in child. If there was no proxy living with the patient, proxy screening was used to determine whether another person met our criteria. If there was no identifiable proxy, the patient was ineligible. Experienced research nurses underwent extensive training and standardization, including interrater reliability assessments for all key measures. They were blinded to the research questions and hypotheses. The proxy interviews included questions on demographics, hearing and vision impairment, alcohol use, smoking, and depression.¹⁶ To evaluate the prevalence of dementia, we used the short form of the Informant Questionnaire on Cognitive Decline in the Elderly (IQCODE).^{17,18} Previous studies^{18,19} that used this instrument have demonstrated its validity compared with cognitive testing of patients. We have previously documented its usefulness in ICU patients.¹⁴ Baseline function was assessed with the Katz Activities of Daily Living Scale²⁰ and higher-level function with Lawton's Instrumental Activities of Daily Living Scale.²¹

Medical records were reviewed to obtain demographic data, diagnosis, Charlson Comorbidity Index score,²² medications on ICU admission, and evidence of depression. Medical records were also reviewed for data immediately before ICU admission in the emergency department (ED) or other areas of the hospital or on day 1 of the ICU stay to obtain information about receipt of benzodiazepines and narcotics. This information was used to calculate the Acute Physiology and Chronic Health Evaluation II (APACHE II) score²³ and the following admission data: serum urea nitrogen level, prothrombin time, partial thromboplastin time, alanine aminotransferase level, aspartate aminotransferase level, direct and total bilirubin levels, temperature, heart rate, and respiratory rate. The most abnormal values in the 24 hours surrounding ICU admission were recorded for all laboratory and physiologic data.

DELIRIUM ASSESSMENT

Delirium was assessed Monday through Friday using the Confusion Assessment Method-ICU (CAM-ICU), a standardized, validated instrument, which has been described in detail previously.^{1,24} If the patient was unarousable (Richmond Agitation-Sedation Scale score of -4 or -5)²⁵ or not available for inter-

view at a given time, 2 more attempts were made during the day to perform the CAM-ICU. Medical record review was used to detect delirium on Saturday and Sunday.^{3,26} The whole medical record was reviewed daily for evidence of delirium. The abstractor coded delirium as yes if any key terms or descriptors were present and evidence of acute onset or fluctuation in symptoms was present. Specifically, the abstractor tried to answer the following question: "Is there evidence in the chart of acute confusional state (eg, delirium, mental status change, inattention, disorientation, hallucinations, agitation, inappropriate behavior, etc)?" This method has a positive predictive accuracy of 87% for delirium detection in the ICU.³

MAIN OUTCOME MEASURE

The main outcome measure for this study was delirium within 48 hours of ICU admission. Patients were considered delirious if they were diagnosed as having delirium by either the CAM-ICU or medical record review.

DEFINITION OF VARIABLES

Variables were considered potential factors associated with delirium on the basis of previously published literature and clinical experience. Patients were considered to have dementia if their IQCODE score was greater than 3.3; this cut point achieves a balance between sensitivity and specificity for detecting dementia.^{14,19,27} Patients were considered to have depression if either the proxy respondent or medical record review was positive for treatment of depression. Comorbidity was evaluated by the Charlson Comorbidity Index²² and the chronic health items of APACHE II.^{23,28} We used clinically meaningful thresholds to categorize physiologic variables as abnormal, and these cut points are presented in **Table 1**. Because of our interest in examining individual components of APACHE II associated with delirium, the full APACHE II score was not included in the multivariate model. The components of APACHE II that we examined included temperature, mean arterial pressure, heart rate, respiratory rate, oxygenation, arterial pH, sodium level, potassium level, creatinine level, hematocrit, and white blood cell count.

STATISTICAL ANALYSIS

Descriptive statistics were ascertained as appropriate. We examined the unadjusted associations between admission factors and delirium using the likelihood ratio χ^2 statistic. We used logistic regression for our multivariate modeling. Admission factors were considered for inclusion in the multivariate model if they had a prevalence of 10% or greater, a likelihood ratio χ^2 greater than 1.64 ($P < .20$), and clinical significance. If a pair of factors produced a correlation coefficient greater than 0.4, the factor with the strongest association with delirium was selected for inclusion in the multivariate model. Variables that were significant in unadjusted analysis but not included in the multivariate model because of correlation with other variables included admission from a nursing home (correlated with activities of daily living) and an alanine aminotransferase level higher than 40 U/L (correlated with an aspartate aminotransferase level > 40 U/L [to convert alanine aminotransferase and aspartate aminotransferase to microkatal per liter, multiply by 0.0167]). The one exception was activities of daily living and dementia, which were correlated at 0.43, but both were included because of the unique clinical information each offers. We also included a marker of dehydration (ratio of serum urea nitrogen to creatinine > 18) and a marker of renal dysfunction (creatinine > 2 mg/dL [to convert to micromoles per liter, multiply by 88.4]). These 2 variables were not strongly correlated (Kendall τ rank correlation coefficient = -0.11).

Table 1. Admission Characteristics Between Patients With and Without Delirium in the First 48 Hours of ICU Admission^a

Risk Factor	Delirium Present (n = 214)	Delirium Absent (n = 90)	P Value
Baseline demographics			
Age, mean ± SD, y	74.5 (8.6)	75.1 (8.1)	.60
Male sex	97 (45.3)	46 (51.1)	.36
Nonwhite race	39 (18.2)	11 (12.2)	.19 ^b
Medicaid status	34 (15.9)	8 (8.9)	.09 ^b
Currently married	102 (47.7)	50 (55.6)	.21
Education, mean ± SD, y ^c	12.4 (2.8)	12.6 (2.7)	.48
Admitted from nursing home	45 (21.0)	10 (11.1)	.03
Baseline medical status			
Vision impairment ^c	25 (11.7)	7 (7.8)	.29
Hearing impairment ^c	37 (17.3)	15 (16.7)	.89
Alcohol use ^c	79 (36.9)	41 (45.6)	.19 ^b
Tobacco use ^c	142 (66.4)	60 (66.7)	.96
History of depression (surrogate or medical record)	71 (33.2)	14 (15.6)	.001 ^b
Dementia by IQCODE score > 3.3 ^c	86 (40.2)	8 (8.9)	<.001 ^b
Charlson Comorbidity Index score, mean ± SD ^c	1.8 (1.9)	1.8 (1.9)	.77
APACHE II score, mean ± SD	24.7 (6.1)	20.0 (5.6)	<.001
APACHE II chronic health evaluation score (scale, 0-9), mean ± SD	0.9 (0.9)	0.6 (0.7)	.008 ^b
Any impairment in activities of daily living	92 (43.0)	18 (20.0)	<.001 ^b
Any impairment in instrumental activities of daily living	186 (86.9)	74 (82.2)	.30
Full code status on ICU admission	182 (85.0)	78 (86.7)	.71
Medication use			
History of benzodiazepines or narcotics as an outpatient	60 (28.0)	15 (16.7)	.03 ^b
Receipt of benzodiazepines before ICU admission	70 (32.7)	11 (12.2)	<.001 ^b
Receipt of narcotics before ICU admission	46 (21.5)	14 (15.6)	.23
Admitting diagnosis			
Respiratory	114 (53.3)	39 (43.3)	.11 ^b
Gastrointestinal hemorrhage	24 (11.2)	28 (31.1)	<.001
Sepsis	36 (16.8)	14 (15.6)	.78
Neurologic	5 (2.3)	0	.06 ^b
Other causes ^d	35 (16.4)	9 (10.0)	.14 ^b
Admitting physiologic variables			
Heart rate > 110/min	114 (53.3)	39 (43.3)	.11 ^b
Respiratory rate > 25/min	143 (66.8)	53 (58.9)	.19 ^b
Temperature > 38.5°C	35 (16.4)	9 (10.0)	.14 ^b
Mean arterial pressure, mean ± SD, mm Hg	58.6 (14.1)	63.5 (16.5)	.009 ^b
Admitting laboratory data			
Serum sodium, mean ± SD, mEq/L	139.7 (5.4)	138.4 (4.2)	.04 ^b
Serum potassium, mean ± SD, mEq/L	4.7 (0.9)	4.4 (0.7)	.02 ^b
Serum creatinine > 2 mg/dL	79 (36.9)	20 (22.2)	.011 ^b
Ratio of serum urea nitrogen to creatinine > 18	148 (69.2)	54 (60.0)	.12 ^b
Arterial pH < 7.35 ^c	129 (60.3)	31 (34.4)	.14 ^b
PaO ₂ :FiO ₂ ratio < 300 ^c	145 (67.8)	42 (46.7)	.88
Serum bicarbonate "high" indicator (> 26 mEq/L), mEq/L	62 (29.0)	20 (22.2)	.22
Serum bicarbonate "low" indicator (< 20 mEq/L), mEq/L	57 (26.6)	18 (20.0)	.21
Hematocrit, mean ± SD, %	32.6 (7.7)	31.7 (8.1)	.36
White blood cell count > 12 000/μL	134 (62.6)	45 (50.0)	.04 ^b
Prothrombin time, mean ± SD, s ^c	14.5 (3.8)	14.4 (3.7)	.86
Partial thromboplastin time, mean ± SD, s ^c	36.6 (19.2)	33.0 (15.5)	.11 ^b
Alanine aminotransferase > 40 U/L ^c	55 (25.7)	11 (12.2)	.03
Aspartate aminotransferase > 40 U/L ^c	85 (39.7)	20 (22.2)	.02 ^b
Direct bilirubin, mean ± SD, mg/dL ^c	0.5 (1.5)	0.6 (1.4)	.69
Total bilirubin, mean ± SD, mg/dL ^c	1.0 (2.1)	1.2 (1.9)	.54

Abbreviations: APACHE, Acute Physiology and Chronic Health Evaluation; FiO₂, fraction of inspired oxygen; ICU, intensive care unit; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly.

SI conversion factors: To convert creatinine to micromoles per liter, multiply by 88.4; alanine aminotransferase to microkats per liter, multiply by 0.0167; aspartate aminotransferase to microkats per liter, multiply by 0.0167; bilirubin to micromoles per liter, multiply by 17.104.

^aData are presented as number (percentage) of patients except where indicated.

^bVariables included in the multivariate model.

^cMissing data were present for some patients as follows: education, 8; vision impairment, 1; hearing impairment, 4; alcohol use, 3; tobacco use, 2; dementia (due to missing items on the IQCODE), 3; Charlson Comorbidity Index score, 1; arterial pH, 49; PaO₂:FiO₂ ratio, 52; prothrombin time, 10; partial thromboplastin time, 13; alanine aminotransferase, 57; aspartate aminotransferase, 57; direct bilirubin, 60; and total bilirubin, 57.

^dOther causes include diabetes mellitus, metabolic abnormalities, acute renal failure, and cardiac causes.

Several of our risk factors had missing data (see the footnote to Table 1) The nature of missing data was investigated by conducting screening tests (ie, Little's test for data missing completely at random and the Troxel Index of Sensitivity to Non-

ignorability).^{29,30} Results of these tests warranted the use of sequential generalized regression to impute missing values for binary variables.³¹ After missing values were multiply imputed, forward selection was used for our multivariate model. Good-

Table 2. Multivariate Model of Admission Risk Factors Associated With Delirium in the First 48 Hours of ICU Admission

Risk Factor	Odds Ratio (95% Confidence Interval)	P Value
Dementia by IQCODE > 3.3	6.3 (2.9-13.8)	< .001
Receipt of benzodiazepines before ICU admission	3.4 (1.6-7.0)	.001
Creatinine > 2 mg/dL	2.1 (1.1-4.0)	.02
Arterial pH < 7.35	2.1 (1.1-3.9)	.02

Abbreviations: ICU, intensive care unit; IQCODE, Informant Questionnaire on Cognitive Decline in the Elderly.

ness of fit was verified by examination of model residuals and with the Hosmer-Lemeshow statistic, both of which were satisfactory. We assessed model discrimination by estimating the area under the receiver operating characteristic curve using a C statistic. The random X sampling bootstrapping procedure was used to measure potential bias in the parameter estimates.³² All statistical tests were 2-tailed, with $P < .05$ indicating statistical significance. Statistical analyses were performed with SAS statistical software, version 9.1.3,³³ and S-Plus software, version 7.0.³⁴

SI UNIT CONVERSION FACTORS

To convert alanine aminotransferase and aspartate aminotransferase to microkatal per liter, multiply by 0.0167; bilirubin to micromoles per liter, multiply by 17.104; and creatinine to micromoles per liter, multiply by 88.4.

RESULTS

Of the 304 patients, delirium occurred in 214 (70.4%) within 48 hours of ICU admission. Of the 214 delirious patients, 152 (71.0%) were delirious on the day of ICU admission; 163 (53.6%) of the 304 patients received mechanical ventilatory assistance at some point during their ICU stay (mean \pm SD length of mechanical ventilation, 4.88 ± 8.4 days). Table 1 presents admission characteristics for participants with and without delirium. The mean age was 75 years, with 47.0% male and 18.1% admitted from a nursing home. In unadjusted analyses, delirium was associated with dementia, history of depression, impairment in activities of daily living, higher APACHE II scores, outpatient use of benzodiazepines or narcotics, and use of benzodiazepines before ICU admission (ie, in the ED). Patients with a lower mean arterial pressure were more likely to have delirium. Of admission laboratory variables, the following were significantly associated with delirium in unadjusted analyses: high sodium level, high potassium level, high creatinine level, high white blood cell count, and high levels of alanine aminotransferase and aspartate aminotransferase.

Table 2 indicates the 4 admission risk factors in the final multivariate model. A history of dementia (IQCODE score > 3.3) had the strongest association with delirium. Also associated with delirium were receipt of benzodiazepines before ICU admission, creatinine level greater than 2 mg/dL, and arterial pH less than 7.35.

The mean value of the C statistic was 0.78, which indicates that the model has a fair amount of explanatory power to predict ICU delirium using the risk factors identified.³⁵ As a measure of reproducibility, bootstrapping confirmed the magnitude and significance of the model parameter estimates.

COMMENT

Although critically ill patients often have multiple risk factors for delirium, our study highlights which admission factors are most important. Previous studies^{9,10,36-41} have examined risk factors for delirium; however, our study is unique in examining an older ICU population and focusing on admission factors to identify patients at greatest risk. We examined delirium occurrence within the first 48 hours of ICU admission to reduce the impact of ICU-related factors on delirium development. The identified factors have strong face validity as risk factors for delirium. Our results include previously identified risk factors for delirium, including dementia and benzodiazepine use, but also identify new factors such as elevated creatinine level and low pH.

Dementia, present in 30.9% of the cohort, was the strongest risk factor for delirium in our study. This finding agrees with previous studies,^{2,10,42-46} which have demonstrated that dementia is an important risk factor for delirium. Despite its importance, dementia is not screened for on ICU admission, and ICU physicians are often unaware of their patients' preexisting dementia.^{14,15} Although dementia is not a modifiable factor, given its high prevalence in this population and its association with delirium, we recommend screening for dementia in all older ICU patients. Knowledge of a patient's dementia status will make ICU staff more cognizant of the potential for delirium, and factors known to contribute to delirium, such as restraints and anticholinergic drugs, can be avoided when possible.

We examined whether outpatient use of benzodiazepines or narcotics was a precipitant for delirium, our hypothesis being that withdrawal of these medications might cause delirium. Although use of these medications as an outpatient was significant in unadjusted analysis, it was not in the multivariate model.

This is the first study, to our knowledge, to examine the association between medications received immediately before admission (ie, in the ED or other parts of the hospital) and ICU delirium. In all, 26.6% of patients received a benzodiazepine before ICU admission and 19.7% received a narcotic. The association between narcotics and delirium is inconsistent; some studies demonstrate a positive association and others show no association.^{9,10,40,45-48} Some studies^{40,49,50} also suggest that untreated pain is a risk factor for delirium. Receipt of narcotics before ICU admission was not associated with delirium in our cohort. Similar to our results, the 1 previous ICU study¹² to examine narcotics and delirium found no association. These findings are limited because we do not have data on indications for narcotic use or objective pain assessments. Benzodiazepines have been associated with delirium in other studies.^{12,51,52} Receipt of benzodiazepines before ICU admission was a significant risk factor for delirium in our

study in both unadjusted and adjusted analyses.

Severity of illness has been associated with delirium in multiple non-ICU studies.^{10,37,44} In unadjusted analysis, the APACHE II score was strongly associated with delirium. Several components of APACHE II were significant in unadjusted analysis, including the chronic health component, mean arterial pressure, white blood cell count, potassium level, sodium level, and creatinine level. Of these components, only arterial pH less than 7.35 and creatinine level greater than 2 mg/dL were retained in the final multivariate model, suggesting that both acidemia and renal failure play important roles in delirium. No other studies have evaluated these 2 factors for delirium development. Their presence in our multivariate model suggests that early attention to correction of acidemia and renal dysfunction may help prevent development, persistence, or severity of delirium in the ICU. This theory should be evaluated in future studies.

Dehydration has been documented to be a risk factor for delirium in non-ICU populations.^{10,44,53} In our study, a ratio of serum urea nitrogen to creatinine greater than 18 was used as a marker of dehydration but was not associated with delirium in our final model. A previous study⁵⁴ has documented that early correction of dehydration is associated with prevention of delirium. Studies in the ICU have demonstrated that early and aggressive volume resuscitation can decrease mortality from sepsis, but these studies did not evaluate delirium.⁵⁵ With the institution of early goal-directed fluid therapy in the ED, dehydration may be less important as a risk factor for delirium in our ICU. The association of dehydration and early goal-directed fluid therapy with ICU delirium should be studied further.

Chief strengths of this study are the accurate delirium detection using validated methods that included CAM-ICU and medical record review for delirium and the very high participation rate. In addition, we collected a detailed, clinically rich prospective data set for multiple risk factors using validated instruments. This data set represents the largest collection of data on delirium among older ICU patients to date and is, to our knowledge, the first to examine admission risk factors.

This study was limited by missing data in some of the risk factors, specifically liver function tests and arterial pH. However, we rigorously investigated the nature of the missing data and used appropriate methods to impute missing values. These risk factors were identified in an older medical ICU population. Generalizability to younger populations or other settings, such as surgical ICUs, will need to be examined further. Another limitation is that our medical record review method, although validated in an older population,²⁶ has not been validated in the ICU.

One other group has examined risk for ICU delirium in patients 18 years or older and found that hypertension, alcoholism, severity of illness, and clinical effects of sedative and analgesic drugs were associated with delirium.^{11,13} We do not have data on hypertension, but severity of illness and use of benzodiazepines were risk factors for delirium in our older population. The studies differ in the instruments used to screen for delirium⁵⁶ and their patient populations.

Many factors that arise during the ICU stay undoubtedly contribute to the development and duration of delirium. Examination of these factors was outside the scope of this study. We limited delirium occurrence to the first 48 hours of ICU admission to minimize the effects of ICU factors. Future studies are greatly needed to examine precipitating factors during the ICU stay, such as psychoactive drug use, invasive procedures, and sleep-wake cycle disruption, and to examine their further contribution to baseline risk.

Importantly, at least 3 of the identified risk factors are amenable to intervention. It is possible to target patients with dementia with reorientation strategies that have been previously demonstrated to be effective for delirium prevention.⁵⁴ Patients with acidemia and acute renal failure will be important to target with direct intervention strategies for their metabolic derangements. Continuous assessment of patient need for sedative medications may allow reduction of receipt or dose of these drugs. Future clinical trials will be crucial to test the effectiveness of these intervention strategies.

For ICU physicians it is important to recognize both predisposing and precipitating risk factors for delirium. Interactions between predisposing and precipitating risk factors are likely to be important in delirium occurrence and duration in the ICU. Knowledge of admission characteristics identified herein will aid physicians in identifying and treating those at greatest risk for delirium. In addition, these admission factors are potential stratification variables for future studies of ICU cohorts examining modifiable risk factors such as psychoactive medication use. The high prevalence and significant health impact of these admission risk factors make their identification of critical importance in ICU care.

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